Remarks

Receipt is acknowledged of the Office Action mailed May 1, 2002. Claims 1-24 are pending. Claims 11-18 and 22-24 have been withdrawn from consideration. Thus, claims 1-10 and 19-21 are active in this case with the entry of the above amendment.

A marked-up copy of the claims, as amended, is attached. No new matter is added with the amendments which are fully supported by the specification.

I. Drawings

Applicants acknowledge the Examiner's requirement for new formal drawings. The new drawings are attached hereto.

II. Specification

The Examiner noted the use of the trademarks BigDye Terminator and Stratalinker and noted that they should be capitalized and accompanied by the generic terminology in the specification. The specification has been amended above to put the trademark names in all capitals. The BigDye Terminator trademark has been set forth in such a way that its identity is clear and is therefore sufficiently distinguished from descriptive nouns by capitalization. The Stratalinker product is also clear, and further is a machine, such that it cannot be accompanied by generic terminology.

III. Claim Objections

The Examiner objected to claims 4-10 and 19 under 37 CFR 1.75(c) as allegedly in improper form because a multiple dependent claim must not depend from another multiple dependent claim. Applicants have amended the claims above to correct the multiple dependencies and also directs the Examiner's attention to the Preliminary Amendment filed with this application on January 11, 2001, in which Applicants made these amendments to correct the multiple dependencies. A copy of that Preliminary Amendment as filed is attached hereto.

IV. Claim Rejections

a. 35 U.S.C. 112, second paragraph

The Examiner has rejected claims 1-3, 20 and 21 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for omitting an essential step. The allegedly omitted step is a correlation, or a recapitulation step at the end of the claim which restates the preamble. Claims 1, 20 and 21 have been amended above to include the allegedly omitted step. Withdrawal of this rejection is therefore requested.

b. 35 U.S.C. 103(a)

The Examiner has rejected Claims 1-3, 20 and 21 under 35 U.S.C. §103(a) as being unpatentable over U.S. patent 5,795,770 ('770) in view of the teachings of Ketchum et al. and Fairman et al.

The examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidence based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or

no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

The Examiner asserts that the '770 patent teaches a process for identifying inhibitors or activators of a eukaryotic potassium channel using mutant S. cerevisiae cells with inactivated endogenous potassium channels TRK1 or TRK1 and TRK2, and wherein a eukaryotic heterologous potassium channel is expressed in the mutant cell. The inhibitor or activator is added to the mutant cells and the effect of the inhibitor or activator is determined. A substance may be added in addition to an activator to determine the effect of the substance on the cells in the presence of the activator. However, the Examiner acknowledges that the '770 patent does not teach mutant S. cerevisiae cells inactivated for TOK1.

The Examiner asserts that Ketchum et al. teach that S. cerevisiae cells contain a potassium channel, TOK1, which transports potassium out of S. cerevisiae cells, and that under certain conditions, also transports potassium into S. cerevisiae cells. The Examiner also asserts that Fairman et al. teach that under certain circumstances, TOK1 transports potassium into S. cerevisiae cells, and that mutant S. cerevisiae cells with inactivated endogenous potassium channels TRK1 and TRK2 that also contain a TOK1 potassium channel that transports potassium out of S. cerevisiae cells, and that under certain conditions, also transports potassium into S. cerevisiae cells.

In light of these assertions, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of filing the instant Application to combine the teachings of the '770 patent with the teachings of Ketchum et al. and Fairman et al. to produce the instant claimed invention because, in the Examiner's opinion, the '770 patent teaches that mutant S. cerevisiae cells should have inactivated endogenous potassium uptake channels. Furthermore, the Examiner concludes that one of ordinary skill in the art would have been motivated to combine the teachings of the '770 patent with the teachings of Ketchum et al. and Fairman et al. to produce the instant claimed invention, because, allegedly, the '770 patent teaches that the beneficial and desirable feature of the mutant S. cerevisiae cells was their

inability to transport potassium into S. cerevisiae cells. The Examiner also asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in producing the instant claimed invention.

The Examiner has cited no specific evidence in the references that there was a suggestion to make the proposed combination. The Examiner merely states that it would have been obvious to one of skill in the art to make the combination. This is precisely the type of conclusory statement proscribed by *In re Lee*. Nor has the Examiner provided evidence that there was a motivation in the prior art to make the combination. In fact, the Examiner notes that the '770 patent "taught that the beneficial and desirable feature of the mutant *S. cerevisiae* cells was their inability to transport potassium into *S. cerevisiae* cells." Office Action, page 6. At the same time, the Examiner asserts that "...one of skill in the art would be motivated to inactivate a known potassium uptake transporter in *S. cerevisiae* cells, namely, TOK1 to produce mutant S. cerevisiae cells with inactivated endogenous potassium channels TRK1, TRK2 and TOK1...." However, the Ketchum reference was published in 1995 and the '770 patent was not even filed until 1997. Therefore, TOK1 was a "known potassium uptake transporter" in *S. cerevisiae* cells before the filing date of the '770 patent. So, if it would have been obvious to make the combination, and if there would have been such a motivation, one would expect that the inventors of the '770 patent themselves would have made the combination.

Further, the '770 patent teaches away from the proposed combination. The '770 patent teaches that a mutated S. cerevisiae cell need not be used to examine heterologous potassium channel proteins. In particular, it is explained in lines 41-50 of column 3 of the '770 patent:

> It should be noted, however, that one would not need to delete TRK1 (or TRK1 and TRK2) in order to make the S. cerevisiae cells dependent on the heterologous potassium channels for growth. One could simply isolate uncharacterized mutations in these that have the effect of significantly reducing their function. As such these organisms include a potassium transport defective phenotype transformed with DNA that suppresses the potassium transport defective phenotype in the organism.

Furthermore, Fairman et al. make clear that they overexpressed TOK1 K+ channels using an exogenous promoter. In particular, on page 155, Fairman et al. state that:

> By bacteriological methods, we have shown that hyperexpression of TOK1 increases [K+]in and supports growth. By electrophysiological methods, we have also registered inward K+ currents through the TOK1. Calculations show that this inward current is more than sufficient to provide the K+ needed for yeast cell doubling. However, these experiments were carried out in a contrived situation: hyperexpressing TOK1 in trk1? trk2? cells. Whether channels encoded by single copy TOK1 under normal control and normal promotion takes up significant K+ for yeast cell remains uncertain (emphasis added).

These passages make clear that contrary to the Examiner's assertions, no motivation exists to combine the teachings of these two references, since the '770 patent teaches that a one need not use a trk1? trk2? cell to examine evaluate compounds for their ability to a *S. cerevisiae* cell dependent upon heterologous K+ channel proteins, and Fairman et al. admits that their data is an anomaly due to overexpression of TOK1 and the use of an autologous promoter. Indeed, Fairman et al. implicitly state that TOK1 may not be responsible for any seepage of potassium ions into the intracellular medium. More specifically, on page 153, Fairman et al. state:

> The above experimentation uses yeast cells strongly expressing TOK1 transgenes for plasmids. It is more difficult to demonstrate the possible role of the inward current through TOK1 channels expressed from a single copy chromosomal TOK1. If TOK1 serves as a K+-uptake pathway, one would expect its removal to aggregate the pathology of the trk1? trk2? double mutant. Indeed, when plated on K+ limiting media, the triple knockout tok1? trk1? trk2? grows less well than does the double knockout, trk1? trk2? (Fig. 5). This difference was consistently observed over a range of limited K+ concentrations from 2 to 5 mM.

In other words, even with TRK1, TRK2, and TOK1 knocked out, the cells still grew, which means that potassium ions still entered the cell. Hence, contrary to the Examiner's assertions, knocking out these three genes does ensure a reasonable expectation of success in producing the instant Invention.

Similarly, no motivation or suggestion exists to combine the teachings of the '770 patent with the teachings of Ketchum et al. In Ketchum et al., *Xenopus oocytes* were injected with TOK1 cRNA. The TOK1 proteins were expressed on the surface of the oocytes, and the potential measured across patches of the cell membrane containing TOK1 proteins were measured. However, Ketchum et al. teach nothing with respect to TOK1 in *S. cerevisiae* cells.

Thus, no motivation or suggestion exists in any of these references to combine their teachings as the Examiner has done in making this rejection. Indeed, it appears that Applicants' disclosure has provided the motivation. Accordingly, Applicants conclude that the Examiner impermissibly has engaged in "hindsight" reconstruction by using Applicants' teaching as a blueprint to hunt through the prior art for the claimed elements and combine them as claimed. *In re Zurko*, 111 F.3d 8876, 42 USPQ2d 1476 (Fed. Cir. 1997); *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicants' disclosure." [Interconnect Planning Corporation v. Feil., 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2D 1551, 1554 (Fed. Cir. 1996).

The above rejections call to mind the following instructions from the Federal Circuit:

> virtually all inventions are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. (emphasis added).

Yamanouchi Pharma. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (*citing In re Rouffet,* 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). In the instant case, the Examiner has failed to even identify all of the claim elements in the prior art, much less a suggestion or motivation to combine those elements in a manner so as to have a reasonable expectation of success in creating the claimed invention.

CONCLUSION

In view of the above amendment and remarks, Applicants respectfully request that all objections and rejections be withdrawn and that a notice of allowance be forthcoming. The Examiner is invited to contact the undersigned attorney for Applicants at 202-919-2142 for any reason related to the advancement of this case.

Respectfully submitted,

Date: Nov 1, 2002

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, D.C. 20006-4004
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

Patricia D. Granados
Attorney for Applicants
Reg. No.: 33,683

Customer No. 26633

26633
PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Page 22, line 24: Sequencing: ABI PRISM™red. protokoll/AmpliTaq®FS ¼ **[BigDyeTerminator]** **BIGDYE TERMINATOR**

Page 24, lines 14-19: Place transfer solution (approx. 1 l 10x SSC) into upper reservoir; **[transfor]** **transfer** time: 90 minutes; switch off vacuum, remove nylon membrane and rinse for 5 minutes in 2x SSC, then leave to dry in the air between filter paper. DNA immobilization: place nylon membrane on UV-permeable cling-film and apply probe at the edge as positive control; place into the **[UV stratalinker]** **STRATALINKER® UV CROSSLINKER** and start crosslinking (1200000 J → 0); membrane may be stored in cling-film or between Whatman filter paper at room temperature or 4°C.

In the Claims:

1. (Amended) A process for identifying inhibitors of a eukaryotic potassium channel, in which
   a) a mutated S. cerevisiae cell is used which does not express the three endogenous potassium channels TRK1, TRK2 and TOK1;
   b) a eukaryotic potassium channel is expressed heterologously in this mutated S. cerevisiae cell;
   c) the mutated S. cerevisiae cell is incubated together with a substance to be tested; and
   d) the effect of the substance to be tested on the eukaryotic potassium channel is determined

   wherein a decrease in the transport of potassium across the eukaryotic potassium channel indicates that the substance is an inhibitor of the eukaryotic potassium channel.

3. (Amended) The process as claimed in **[one or more of claims 1 and 2] claim 1**, wherein the eukaryotic potassium channel is a human potassium channel.

4. (Amended) The process as claimed in **[one or more of claims 1 to]claim** 3, wherein the eukaryotic potassium channel is a HERG1, Kv1.5 or gpIRK1.

5. (Amended) The process as claimed in **[one or more of claims 1 to] claim** 4, wherein the eukaryotic potassium channel is mutated.

6. (Amended) The process as claimed in **[one or more of claims 1 to]claim** 5, wherein the eukaryotic potassium channel is present in a yeast expression plasmid.

7. (Amended) The process as claimed in **[one or more of claims 1 to]claim** 6, wherein the mutated S. cerevisiae cell expresses constitutively a growth reporter.

8. (Amended) The process as claimed in **[one or more of claims 1 to]claim** 7, wherein a substance to be tested, which has an effect on the eukaryotic potassium channel, inhibits the growth of the mutated S. cerevisiae cell.

9. (Amended) The process as claimed in **[one or more of claims 1 to]claim** 7, wherein the effect of a substance to be tested on the eukaryotic potassium channel is determined by measuring the cell count of the mutated S. cerevisiae cells.

19. (Amended) The use of a mutated S. cerevisiae cell as claimed in **[one or more of claims 11 to]claim** 17 for identifying substances which inhibit the activity of the eukaryotic potassium channel.

20. (Amended) A process of identifying activators of a eukaryotic potassium channel, in which

a) a mutated S. cerevisiae cell is used which does not express the three

endogenous potassium channels TRK1, TRK2 and TOK1;

b) a eukaryotic potassium channel is expressed heterologously in this mutated S. cerevisiae cell;

c) the mutated S. cerevisiae cell is incubated together with a substance to be tested; and

d) the effect of the substance to be tested on the eukaryotic potassium channel is determined

wherein an increase in the transport of potassium across the eukaryotic potassium channel indicates that the substance is an activator of the eukaryotic potassium channel.

21. (Amended) A process of identifying activators of a eukaryotic potassium channel, in which

a) a mutated S. cerevisiae cell is used which does not express the three endogenous potassium channels TRK1, TRK2 and TOK1;

b) a eukaryotic potassium channel is expressed heterologously in this mutated S. cerevisiae cell;

c) the mutated S. cerevisiae cell is incubated together with a substance to be tested in the presence of an inhibitor of the eukaryotic potassium channel; and

d) the effect of the substance to be tested on the eukaryotic potassium channel is determined

wherein an increase in the transport of potassium across the eukaryotic potassium channel indicates that the substance is an activator of the eukaryotic potassium channel.